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AB Ag encounter in the absence of proliferation results in the establishment of T cell unresponsiveness, also known as **T cell clonal anergy**. Anergic T cells fail to proliferate upon restimulation because of the inability to produce IL-2 and to properly regulate the

G(1) cell cycle checkpoint. Because optimal TCR and CD28 engagement can elicit IL-2-independent cell cycle progression, we investigated whether CD3/CD28-mediated activation of anergic T cells could overcome G(1) cell cycle block, drive T cell proliferation, and thus reverse clonal anergy. We show here that although antigenic stimulation fails to elicit

G(1)-to-S transition, anti-CD3/CD28 mAbs allow proper cell cycle progression and proliferation of anergic T cells. However, CD3/CD28-mediated cell

division does not restore Ag responsiveness. Our data instead indicate that reversal of clonal anergy specifically requires an IL-2-dependent, **rapamycin**-sensitive signal, which is delivered independently of cell proliferation. Thus, by tracing proliferation and Ag responsiveness of individual cells, we show that whereas both TCR/CD28 and

IL-2-generated signals can drive T cell proliferation, only IL-2/IL-2R interaction regulates Ag responsiveness, indicating that proliferation and clonal anergy can be independently regulated.